

CLAIMS

1. A selective suppressor of the IgE production comprising a compound which suppresses the IgE production in a process from a differentiation of a mature B cell into an antibody-producing cell to the production of an antibody and which does not suppress or weakly suppresses the production of IgG, IgM and/or IgA which are produced at the same time.

2. The selective suppressor of the IgE production claimed in claim 1, wherein a suppression of the IgE production is 10,000 times or more that of the IgG, IgM and/or IgA production.

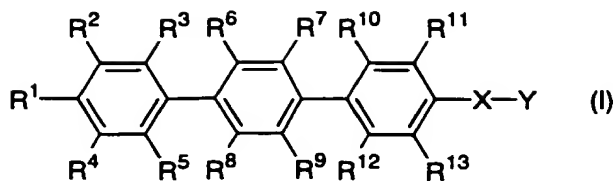
3. The selective suppressor of the IgE production claimed in claim 1 which does not suppress 50 % or more of the IgG, IgM and/or IgA production even at 10,000 times of the concentration at which 50 % of the IgE production is suppressed as compared with that in the absence of the suppressor.

4. The selective suppressor of the IgE production claimed in claim 1, 2 or 3 which suppresses 90 % or more of the IgE production, as compared with that without administration of the suppressor, at which dosage the suppressor does not suppress or weakly suppresses the IgM, IgG and/or IgA production when the suppressor is administered to a mammal sensitized by an allergen.

A 5. The selective suppressor of the IgE production claimed in claim 1, 2, ^{or 3} ~~3 or 4~~ which suppresses infiltration of an inflammatory cell to tissue.

6. The selective suppressor of the IgE production claimed in claim 5 wherein the inflammatory cell is an eosinophil and/or a neutrophile.

7. A compound of the formula (I):



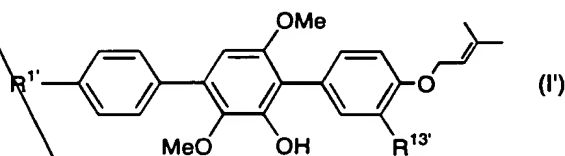
wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is $-O-$, $-CH_2-$, $-NR^{14}$, wherein R^{14} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or $-S(O)_p$ wherein p is an integer of 0 to 2, Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is $-CH_2-$ and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is $-O-$ or $-NR^{14}$,

R^1 and R^4 , R^1 and R^2 , R^2 and R^3 , R^4 and R^5 , R^6 and R^7 , R^8 and R^9 , R^{10} and R^{11} , R^{12} and R^{13} , R^{11} and $-X-Y$, or R^{13} and $-X-Y$ taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR^{15} wherein R^{15} is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl and which may optionally be substituted,

excluding compounds wherein one or more of R^6, R^7, R^8 and R^9 are halogen and the

others are hydrogen, compounds wherein all of R⁶, R⁷, R⁸ and R⁹ are halogen and compounds wherein all of R²-R¹³ are hydrogen, halogen or cyano, provided that R¹ is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R², R³, R⁴, R⁵ and R¹² are hydrogen, or R¹³ is not hydrogen or halogen when R⁶, R⁷, R⁸ and R⁹ are all simultaneously hydrogen, and further provided that R¹ is not methyl or acetyloxy, R¹³ is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl, or -X-Y is not methoxy when at least one of R⁶, R⁷, R⁸ and R⁹ is a substituent other than hydrogen, and excluding a compound of the formula (I'):



wherein R^{1'} is hydrogen or hydroxy and R^{13'} is hydroxy or methoxy, pharmaceutically acceptable salt, hydrate or prodrug thereof.

8. The compound claimed in claim 7 wherein R¹ is hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyloxy, lower alkylsulfonyl, formyl, optionally substituted amino, lower alkylsulfinyl, acyloxy, nitro, cyano, optionally substituted sulfamoyl or heterocyclyl, R² is hydrogen, hydroxy, halogen, optionally substituted lower alkyl or optionally substituted lower alkylsulfonyloxy, R³ is hydrogen, hydroxy, halogen or optionally substituted lower alkoxy, R⁴ is hydrogen, optionally substituted lower alkyl, halogen, optionally substituted lower alkoxy, nitro or optionally substituted amino, R⁵ is hydrogen, optionally substituted lower alkoxy, lower alkoxycarbonyl or carboxy,

R⁶ is hydrogen, halogen, optionally substituted lower alkyl, carboxy, lower alkoxy, carbonyl, nitro, formyl, amino or lower alkylsulfonyloxy,

R⁷ and R⁸ are each independently hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, formyl or optionally substituted amino,

R⁹ is hydrogen, hydroxy, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkoxy, carbonyl, nitro, formyl, amino or lower alkylsulfonyloxy, optionally substituted carbonyl or optionally substituted amino,

R¹⁰ is hydrogen or lower alkoxy,

R¹¹ is hydrogen, halogen, optionally substituted lower alkyl, carboxy, lower alkoxy, carbonyl, nitro, formyl, amino or lower alkylsulfonyloxy,

R¹² is hydrogen,

R¹³ is hydroxy, halogen, carboxy, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted acyloxy, optionally substituted lower alkylsulfonyloxy, formyl, nitro or optionally substituted amino,

Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl or optionally substituted cycloalkenyl and Y may be optionally substituted lower alkoxy, carbonyl, nitro, formyl, amino or lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or -NR¹⁴,

and R¹ and R², R¹ and R⁴, R⁸ and R⁹, R¹¹ and -X-Y, or R¹ and -X-Y taken together may form a 5- or 6-membered ring which contains one or more of O or NR¹⁵ wherein R¹⁵ is the same as defined in claim 7 and which may optionally be substituted, pharmaceutically acceptable salt, hydrate or prodrug thereof.

9. The compound, pharmaceutically acceptable salt or hydrate thereof claimed in

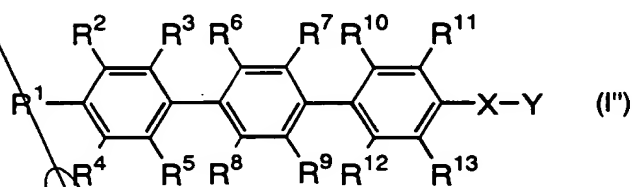
claim 7 or 8 which has an immunosuppressive effect.

10. The pharmaceutical composition comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claim 7 or 8.

11. An immunosuppressor comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claim 7 or 8.

12. An anti-allergic agent comprising the compound, pharmaceutically acceptable salt, hydrate or prodrug thereof claimed in claim 7 or 8.

13. An immunosuppressor comprising a compound of the formula (I''):



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are each independently hydrogen, hydroxy, halogen, carboxy, optionally substituted lower alkyl optionally substituted, lower alkoxy, optionally substituted lower alkenyl, optionally substituted lower alkenyloxy, optionally substituted lower alkylthio, optionally substituted lower alkoxycarbonyl, optionally substituted acyloxy, optionally substituted lower alkylsulfonyl, optionally substituted lower alkylsulfonyloxy, optionally substituted lower alkylsulfinyl, nitro, cyano, formyl, optionally substituted amino, optionally substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, -CH₂-, -NR¹⁴, wherein R¹⁴ is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(O)_p- wherein p is an integer of 0 to 2, Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is -CH₂- and may

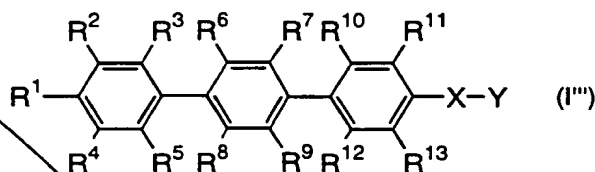
COC1=C(C(=C(C=C1)C(=C2C=C(C=C2)C=C3C=C(C=C3)OC/C=C/C=C4C=C(C)C)C4)C(=C5C=C(C=C5)O)C=C6C=C(C=C6)C=C7C=C(C=C7)C=C8C=C(C=C8)C=C9C=C(C=C9)C=C10C=C(C=C10)C=C11C=C(C=C11)C=C12C=C(C=C12)C=C13C=C(C=C13)C=C14C=C(C=C14)C=C15C=C(C=C15)C=C16C=C(C=C16)C=C17C=C(C=C17)C=C18C=C(C=C18)C=C19C=C(C=C19)C=C20C=C(C=C20)C=C21C=C(C=C21)C=C22C=C(C=C22)C=C23C=C(C=C23)C=C24C=C(C=C24)C=C25C=C(C=C25)C=C26C=C(C=C26)C=C27C=C(C=C27)C=C28C=C(C=C28)C=C29C=C(C=C29)C=C30C=C(C=C30)C=C31C=C(C=C31)C=C32C=C(C=C32)C=C33C=C(C=C33)C=C34C=C(C=C34)C=C35C=C(C=C35)C=C36C=C(C=C36)C=C37C=C(C=C37)C=C38C=C(C=C38)C=C39C=C(C=C39)C=C40C=C(C=C40)C=C41C=C(C=C41)C=C42C=C(C=C42)C=C43C=C(C=C43)C=C44C=C(C=C44)C=C45C=C(C=C45)C=C46C=C(C=C46)C=C47C=C(C=C47)C=C48C=C(C=C48)C=C49C=C(C=C49)C=C50C=C(C=C50)C=C51C=C(C=C51)C=C52C=C(C=C52)C=C53C=C(C=C53)C=C54C=C(C=C54)C=C55C=C(C=C55)C=C56C=C(C=C56)C=C57C=C(C=C57)C=C58C=C(C=C58)C=C59C=C(C=C59)C=C60C=C(C=C60)C=C61C=C(C=C61)C=C62C=C(C=C62)C=C63C=C(C=C63)C=C64C=C(C=C64)C=C65C=C(C=C65)C=C66C=C(C=C66)C=C67C=C(C=C67)C=C68C=C(C=C68)C=C69C=C(C=C69)C=C70C=C(C=C70)C=C71C=C(C=C71)C=C72C=C(C=C72)C=C73C=C(C=C73)C=C74C=C(C=C74)C=C75C=C(C=C75)C=C76C=C(C=C76)C=C77C=C(C=C77)C=C78C=C(C=C78)C=C79C=C(C=C79)C=C80C=C(C=C80)C=C81C=C(C=C81)C=C82C=C(C=C82)C=C83C=C(C=C83)C=C84C=C(C=C84)C=C85C=C(C=C85)C=C86C=C(C=C86)C=C87C=C(C=C87)C=C88C=C(C=C88)C=C89C=C(C=C89)C=C90C=C(C=C90)C=C91C=C(C=C91)C=C92C=C(C=C92)C=C93C=C(C=C93)C=C94C=C(C=C94)C=C95C=C(C=C95)C=C96C=C(C=C96)C=C97C=C(C=C97)C=C98C=C(C=C98)C=C99C=C(C=C99)C=C100C=C(C=C100)C=C101C=C(C=C101)C=C102C=C(C=C102)C=C103C=C(C=C103)C=C104C=C(C=C104)C=C105C=C(C=C105)C=C106C=C(C=C106)C=C107C=C(C=C107)C=C108C=C(C=C108)C=C109C=C(C=C109)C=C110C=C(C=C110)C=C111C=C(C=C111)C=C112C=C(C=C112)C=C113C=C(C=C113)C=C114C=C(C=C114)C=C115C=C(C=C115)C=C116C=C(C=C116)C=C117C=C(C=C117)C=C118C=C(C=C118)C=C119C=C(C=C119)C=C120C=C(C=C120)C=C121C=C(C=C121)C=C122C=C(C=C122)C=C123C=C(C=C123)C=C124C=C(C=C124)C=C125C=C(C=C125)C=C126C=C(C=C126)C=C127C=C(C=C127)C=C128C=C(C=C128)C=C129C=C(C=C129)C=C130C=C(C=C130)C=C131C=C(C=C131)C=C132C=C(C=C132)C=C133C=C(C=C133)C=C134C=C(C=C134)C=C135C=C(C=C135)C=C136C=C(C=C136)C=C137C=C(C=C137)C=C138C=C(C=C138)C=C139C=C(C=C139)C=C140C=C(C=C140)C=C141C=C(C=C141)C=C142C=C(C=C142)C=C143C=C(C=C143)C=C144C=C(C=C144)C=C145C=C(C=C145)C=C146C=C(C=C146)C=C147C=C(C=C147)C=C148C=C(C=C148)C=C149C=C(C=C149)C=C150C=C(C=C150)C=C151C=C(C=C151)C=C152C=C(C=C152)C=C153C=C(C=C153)C=C154C=C(C=C154)C=C155C=C(C=C155)C=C156C=C(C=C156)C=C157C=C(C=C157)C=C158C=C(C=C158)C=C159C=C(C=C159)C=C160C=C(C=C160)C=C161C=C(C=C161)C=C162C=C(C=C162)C=C163C=C(C=C163)C=C164C=C(C=C164)C=C165C=C(C=C165)C=C166C=C(C=C166)C=C167C=C(C=C167)C=C168C=C(C=C168)C=C169C=C(C=C169)C=C170C=C(C=C170)C=C171C=C(C=C171)C=C172C=C(C=C172)C=C173C=C(C=C173)C=C174C=C(C=C174)C=C175C=C(C=C175)C=C176C=C(C=C176)C=C177C=C(C=C177)C=C178C=C(C=C178)C=C179C=C(C=C179)C=C180C=C(C=C180)C=C181C=C(C=C181)C=C182C=C(C=C182)C=C183C=C(C=C183)C=C184C=C(C=C184)C=C185C=C(C=C185)C=C186C=C(C=C186)C=C187C=C(C=C187)C=C188C=C(C=C188)C=C189C=C(C=C189)C=C190C=C(C=C190)C=C191C=C(C=C191)C=C192C=C(C=C192)C=C193C=C(C=C193)C=C194C=C(C=C194)C=C195C=C(C=C195)C=C196C=C(C=C196)C=C197C=C(C=C197)C=C198C=C(C=C198)C=C199C=C(C=C199)C=C200C=C(C=C200)C=C201C=C(C=C201)C=C202C=C(C=C202)C=C203C=C(C=C203)C=C204C=C(C=C204)C=C205C=C(C=C205)C=C206C=C(C=C206)C=C207C=C(C=C207)C=C208C=C(C=C208)C=C209C=C(C=C209)C=C210C=C(C=C210)C=C211C=C(C=C211)C=C212C=C(C=C212)C=C213C=C(C=C213)C=C214C=C(C=C214)C=C215C=C(C=C215)C=C216C=C(C=C216)C=C217C=C(C=C217)C=C218C=C(C=C218)C=C219C=C(C=C219)C=C220C=C(C=C220)C=C221C=C(C=C221)C=C222C=C(C=C222)C=C223C=C(C=C223)C=C224C=C(C=C224)C=C225C=C(C=C225)C=C226C=C(C=C226)C=C227C=C(C=C227)C=C228C=C(C=C228)C=C229C=C(C=C229)C=C230C=C(C=C230)C=C231C=C(C=C231)C=C232C=C(C=C232)C=C233C=C(C=C233)C=C234C=C(C=C234)C=C235C=C(C=C235)C=C236C=C(C=C236)C=C237C=C(C=C237)C=C238C=C(C=C238)C=C239C=C(C=C239)C=C240C=C(C=C240)C=C241C=C(C=C241)C=C242C=C(C=C242)C=C243C=C(C=C243)C=C244C=C(C=C244)C=C245C=C(C=C245)C=C246C=C(C=C246)C=C247C=C(C=C247)C=C248C=C(C=C248)C=C249C=C(C=C249)C=C250C=C(C=C250)C=C251C=C(C=C251)C=C252C=C(C=C252)C=C253C=C(C=C253)C=C254C=C(C=C254)C=C255C=C(C=C255)C=C256C=C(C=C256)C=C257C=C(C=C257)C=C258C=C(C=C258)C=C259C=C(C=C259)C=C260C=C(C=C260)C=C261C=C(C=C261)C=C262C=C(C=C262)C=C263C=C(C=C263)C=C264C=C(C=C264)C=C265C=C(C=C265)C=C266C=C(C=C266)C=C267C=C(C=C267)C=C268C=C(C=C268)C=C269C=C(C=C269)C=C270C=C(C=C270)C=C271C=C(C=C271)C=C272C=C(C=C272)C=C273C=C(C=C273)C=C274C=C(C=C274)C=C275C=C(C=C275)C=C276C=C(C=C276)C=C277C=C(C=C277)C=C278C=C(C=C278)C=C279C=C(C=C279)C=C280C=C(C=C280)C=C281C=C(C=C281)C=C282C=C(C=C282)C=C283C=C(C=C283)C=C284C=C(C=C284)C=C285C=C(C=C285)C=C286C=C(C=C286)C=C287C=C(C=C287)C=C288C=C(C=C288)C=C289C=C(C=C289)C=C290C=C(C=C290)C=C291C=C(C=C291)C=C292C=C(C=C292)C=C293C=C(C=C293)C=C294C=C(C=C294)C=C295C=C(C=C295)C=C296C=C(C=C296)C=C297C=C(C=C297)C=C298C=C(C=C298)C=C299C=C(C=C299)C=C300C=C(C=C300)C=C301C=C(C=C301)C=C302C=C(C=C302)C=C303C=C(C=C303)C=C304C=C(C=C304)C=C305C=C(C=C305)C=C306C=C(C=C306)C=C307C=C(C=C307)C=C308C=C(C=C308)C=C309C=C(C=C309)C=C310C=C(C=C310)C=C311C=C(C=C311)C=C312C=C(C=C312)C=C313C=C(C=C313)C=C314C=C(C=C314)C=C315C=C(C=C315)C=C316C=C(C=C316)C=C317C=C(C=C317)C=C318C=C(C=C318)C=C319C=C(C=C319)C=C320C=C(C=C320)C=C321C=C(C=C321)C=C322C=C(C=C322)C=C323C=C(C=C323)C=C324C=C(C=C324)C=C325C=C(C=C325)C=C326C=C(C=C326)C=C327C=C(C=C327)C=C328C=C(C=C328)C=C329C=C(C=C329)C=C330C=C(C=C330)C=C331

A

a (I''), according to claim 13

A

15. A process for producing a compound of the formula (I''):



474

Sub
A2
BT

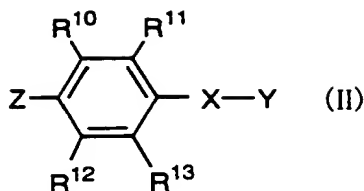
substituted carbamoyl, optionally substituted sulfamoyl or optionally substituted heterocyclyl,

X is -O-, -CH₂-, -NR¹⁴, wherein R¹⁴ is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl or acetyl, or -S(o)p- wherein p is an integer of 0 to 2, Y is optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl or optionally substituted heterocyclyl, and Y may optionally be substituted lower alkoxy when X is -CH₂- and may optionally be substituted lower alkoxycarbonyl, optionally substituted lower alkylsulfonyl or optionally substituted arylsulfonyl when X is -O- or -NR¹⁴,

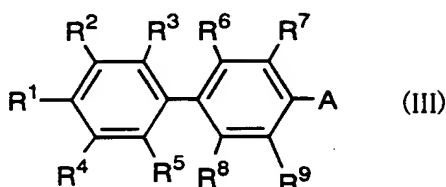
R¹ and R⁴, R¹ and R², R² and R³, R⁴ and R⁵, R⁶ and R⁷, R⁸ and R⁹, R¹⁰ and R¹¹, R¹² and R¹³, R¹¹ and -X-Y, or R¹³ and -X-Y taken together may form a 5- or 6-membered ring which may contain one or more of O, S or NR¹⁵ wherein R¹⁵ is hydrogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted arylsulfonyl, and which may optionally be substituted,

excluding a compound wherein one or more of R⁶, R⁷, R⁸ and R⁹ are halogen and the others are hydrogen, compounds wherein all of R⁶, R⁷, R⁸ and R⁹ are halogen and compounds wherein all of R²-R¹³ are hydrogen, halogen or cyano,

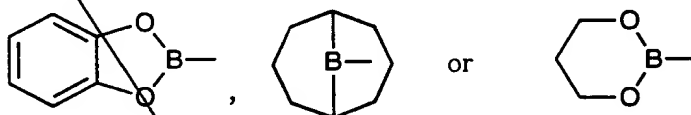
provided that R¹ is not hydrogen, fluorine, optionally substituted lower alkyl or optionally substituted lower alkoxy, all of R², R³, R⁴, R⁵ and R¹² are hydrogen or R¹³ is not hydrogen or halogen when R⁶, R⁷, R⁸ and R⁹ are all simultaneously hydrogen, and further provided that R¹ is not methyl or acetyloxy, R¹³ is not hydrogen, optionally substituted lower alkoxycarbonyl or optionally substituted carbamoyl or -X-Y is not methoxy when at least one of R⁶, R⁷, R⁸ and R⁹ is a substituent other than hydrogen, pharmaceutically acceptable salt or hydrate thereof, which comprises reacting a compound of the formula (II):



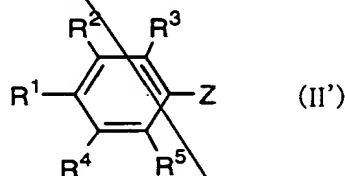
with a compound of the formula (III):



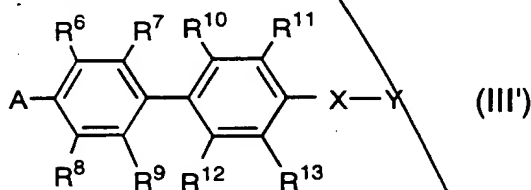
wherein, in the formulas (II) and (III), $R^1 - R^{13}$, X and Y are the same as defined in claim 7, either of A and Z is dihydroxyborane, di(lower)alkoxyborane, di(lower)alkylborane,



and the other is halogen or $-\text{OSO}_2(\text{C}_q\text{F}_{2q+1})-$ wherein q is an integer of 0 to 4, or reacting a compound of the formula (II'):



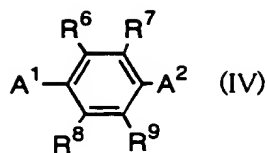
with a compound of the formula (III'):



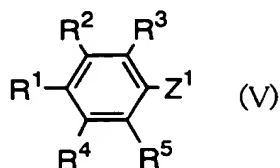
wherein, in the formulas (II') and (III'), $R^1 - R^{13}$, X and Y are the same as defined in claim 7 and A and Z are the same as defined in the above formulas (II) and (III).

16. The process for producing the compound of the formula (I'''), pharmaceutically acceptable salt or hydrate thereof according to claim 15 comprising the reaction of a

compound of the formula (IV):

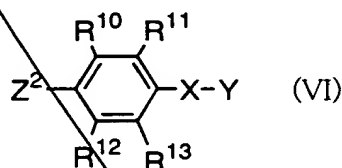


with a compound of the formula (V):



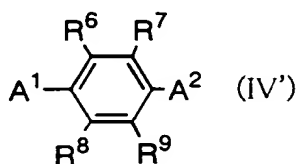
wherein, in the formulas (IV) and (V), R¹ - R⁹ are the same as defined in the formula (I) in claim 7, Z¹ is the same as Z defined in the formula (II) in claim 15, A¹ and A² are each independently the same as A defined in the formula (III) in claim 15, and the reactivity of A¹ is higher than or equal to that of A²,

followed by the reaction with a compound of the formula (VI):



wherein R¹⁰-R¹³, X and Y are the same as defined in the formula (I) in claim 7 and Z² is the same as Z defined in the above formula (II).

17. The process for producing the compound of the formula (I'''), pharmaceutically acceptable salt or hydrate thereof according to claim 15 comprising the reaction of a compound of the formula (IV'):



wherein R⁶-R⁹ is the same as defined in the formula (I) in claim 7, A¹ and A² are each independently the same as A defined in the formula (III) in claim 15, and the reactivity

5th

A2
B1

of A^2 is higher than or equal to that of A^1 ,

with a compound of the formula (VI) in claim 16, followed by the reaction with a

compound of the formula (V) in claim 16.

add

B2

09214277.030199